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BEFORE THE BOARD OF PATENT
APPEALS AND INTERFERENCES

PAPER NO.: 21

Examiner: Low
Art Unit: 1804

Application Serial Number: 08/335,461
Filing Date: 7 November 1994
Appellant(s): Gjerset *et al.*

Anthony C. Chen
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief
on appeal filed on 30 May 1997

This application contains a supplemental disclosure statement filed 13 December 1996 which is after the final Office Action. It has been placed in the file but has not been further considered on the merits. Applicant admits of its noncompliance to 37 C.F.R. 1.98.

(1) Real Party of Interest.

A statement identifying the real party in interest is contained in the brief.

(2) Related appeals and interferences.

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of the claims.

The statement of the status of the claims contained in the brief is incorrect because the statements of the basis of the rejections in this section of the brief on appeal is inappropriate. A corrected statement of the status of the claims is as follows:

The first response after final filed 24 October 1996 has not been entered. Claims 1, 2, 6, 9, 10, 12-15, 17-20 and 22 have been amended subsequent to the final rejection by entry of the amendment after final filed 13 February 1997. Claims 3, 21, and 22 were canceled by the amendment after final filed 13 February 1997. This appeal involves claims 1, 2, and 4-20 and 23 and no claims are allowed.

(4) Status of the Amendments after final.

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect because it is incomplete. A corrected statement follows.

A first amendment after final filed 24 October 1996 was filed. It was not entered for the reasons indicated in the Advisory Action (paper number 11) mailed 12 November 1996. A second amendment after final was submitted 13 February 1997 and was entered as indicated in the Advisory Action (paper number 15) mailed 11 March 1997. Consequently claims 3, 21, and 22 are canceled by the amendment after final filed 13 February 1997.

(5) Summary of the invention.

The summary of the invention in the brief is deficient for the following reasons. The summary does not contain reference to the appropriate pages and line numbers and/or figures. See 37 C.F.R. 1.192(c)(5). Appellant's summary refers to enhancing, however, "enhancing" is not *per se* recited in the appealed claims.

A more concise summary of the invention follows and is defined by the claims on appeal which are considered as one group.

The invention is a method of increasing the effect of a cancer therapy by delivering to a tumor cell lacking a wild-type p53 gene, a gene encoding wild-type p53 (no sequence is defined as the wild-type in the written description), effecting expression of the gene encoding wild-type p53 in said tumor cell and subjecting said tumor cell to cancer therapy.

(6) Issues.

The appellant's statement of the issues in the brief (page 5) is incorrect. The sole issue is that the pending claims 1, 2, 4-20, and 23 are obvious in view of the stated rejections under 35 U.S.C. 103(a). The rejections are:

(A) Claims 1, 2, 4-11, and 17-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2);

(B) Claims 12-18, and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1, 2, 4-11, and 17-20 above and further in view of Wu *et al.* (US 5,166,320) and Malkin *et al.* (Science) and Chen *et al.* (Oncogene);

(C) Claims 1, 2, 4-15, and 17-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nabel *et al.* (US 5,328,470) taken with Wu *et al.* (US 5,166,320), Malkin *et al.* (Science), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2); and,

(D) Claim 23, directed to a species extracted from a Markush group (claim 17 as to an aerosolized preparation) stands rejected under 35 U.S.C. 103(a) as being

unpatentable over either of Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1-11, 17-20, and 22 above;

or,

under 35 U.S.C. 103(a) as being unpatentable over Nabel *et al.* (US 5,328,470) taken with Wu *et al.* (US 5,166,320), Malkin *et al.* (Science), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1, 2, 4-15 and 17-20 above, each further in view of Eppstein *et al.* US 5,366,737).

(7) Grouping of Claims.

The rejection of claims 1, 2, 4-20, and 23 stand or fall together because appellant's brief states the claims are considered in one group. See Appeal Brief at page 6.

(8) Claims Appealed.

The copy of the appealed claims contained in the appendix to the brief is correct.

(9) Prior Art of Record.

The prior art of record relied cited in the rejections of the appealed claims is set forth below.

Cheng *et al.* 1992 Cancer Res. 52: 222-226.

Srivastava US 5,252,479.

Moossa *et al.* (eds.) 1991 in: Comprehensive Textbook of Oncology, Williams & Wilkins, Baltimore, MD, vol. 1, pages 477, 527-536, 565-568, 590-594, 607-612, vol 2, pages 1098, 1138-1140, 1170, 1329, 1368, and 1569-1572.

Wu *et al.* US 5,166,320.

Malkin *et al.* 1990 Science 250: 1233-1238.

Chen *et al.* 1991 Oncogene 6: 1799-1805.

Nabel *et al.* US 5,328,470.

Eppstein *et al.* US 5,366,737.

(10) New Prior Art.

No new prior art has been applied in this examiner's answer.

(11) Grounds of rejection.

The following grounds of rejection under 35 U.S.C. 103(a) are applied to the appealed claims. Note the correction to the citation of "Srivastava (US 749)" which is "Srivastava (US 5,252,479)".

Claims 1, 2, 4-11 and 17-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2).

Cheng *et al.* disclosed suppression of T-cell acute lymphoblastic leukemia (T-ALL) post transfection of T-ALL cells with a vector effecting expression of the p53 gene product (see at least the abstract). The reference indicated therapeutic treatment suppressed unregulated growth of T-ALL cells by introduction of the DNA encoding p53 into cells in conjunction with autologous bone marrow transplantation regimes in an effort to reduce the frequency of posttransplantation relapse. Page 225 of the Cheng *et al.* reference taught expression of the wild-type allele for p53 effected a powerful suppression of the tumorigenic phenotype *in vivo* (i.e., a correlation of the effects) without evidence of significant toxic effects in the cells. Where the Cheng *et al.* reference indicated the vectors provided the DNA encoding wild-type p53, it would have been obvious to one of ordinary skill in the art to have (1) used known vectors and processes demonstrated as effective that are known to function *in vivo* for delivery of known DNA encoding wild-type p53 for which the Srivastava reference disclosed vectors that are safe for gene therapy to; (2) reduced/eliminated factors in the potential problem of heterologous DNA effecting unwanted effects which would have motivated one of ordinary skill in the art; (3) used the teachings and vectors and modifications thereto such as disclosed in the Srivastava patent which at col 3 indicated the vectors are for bone marrow cells, i.e., like those of the Cheng *et al.* reference); and (4) used virus such as an adeno, herpes, or vaccinia virus (see col 3) for delivery of DNA encoding, for example, p53 or Rb(col 6) for treatment of cancer (col 6).

Here, where the Cheng *et al.* reference referred to bone marrow transplantation regimes it would have been obvious to any one of ordinary skill in the art that radiation therapy (as for example Moossa *et al.* at pages 477, 1138, 1140, and 1170), chemotherapy (as for example Moossa *et al.* at pages 527-536, 565-568, 1098, 1140, and 1572), biological therapy (as for example Moossa *et al.* at pages 607-612 using biological response modifiers), cryotherapy (as for example Moossa *et al.* at

pages 1098, 1170, 1329, 1368, and 1569-1570), and hyperthermia (as for example Moossa *et al.* at page 1139-1149) are known treatment methods, have been successfully used, and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent (as for example via an artery (page 590) or a (page 591) body cavity or by IV as for example indicated at page 592). The combined references would have resulted in the claimed process wherein a DNA (i.e., the gene encoding a wild-type p53) encoding a tumor sensitizing product was delivered to an afflicted individual along with routine known and established appropriate therapies (radiation therapy, chemotherapy, biological therapy, cryotherapy, and hyperthermia therapy in one or more combinations) for treatment of cancers. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 12-18, and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1, 2, 4-11 and 17-20 above and further in view of Wu *et al.* (US 5,166,320) and Malkin *et al.* (Science) and Chen *et al.* (Oncogene).

Cheng *et al.* (Cancer Res.), Srivastava, and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) and where the Srivastava reference indicated safe vectors, Wu *et al.* disclosed a process of *in vivo* delivery (as for example intravenous injection, i.e., a direct injection wherein injection into an artery is an obvious variation of injection into a vein) of DNA to a target cell (see for example col 11, and the abstract as to polylysine) using a complex of asialoglycoprotein to hepatoma cells and for replacement of "defective genes" responsible for inherited diseases as for example where there are familial germline mutations of cancer where mutations in the DNA encoding p53 have been shown to be transmitted via the germline (see Malkin *et al.*, the abstract and pages 1234-1238) and where Cheng *et al.* (Cancer Res.) indicate that providing DNA encoding wild-type p53 to cells that have defective or no expression of p53 with subsequent expression of that DNA encoding wild-type p53 effects reduced tumorigenicity (see page 1803) wherein it would have been obvious to one of ordinary skill in the art to combine the teachings of Cheng *et al.* (Cancer Res.) taken with Srivastava, Moossa *et al.* with Wu *et al.*, Malkin *et al.* and Chen *et al.* (Oncogene) for treatment of cancer and directed delivery of the DNA encoding for example p53 to effect reduced tumorigenicity and reduced frequency of

posttransplantation relapse. Here, the Moossa *et al.* reference (page 530) indicated that because there are such narrow margins between effective and toxic dosages for many antineopplastic agents, rational therapy should be assisted by the ability to maintain drug concentrations in the specified therapeutic ranges. Such assist "the ability to maintain drug concentrations in the specified therapeutic ranges" is what anyone of ordinary skill in the art would expect if not anticipate from combinatorial therapy (Moossa *et al.* at pages 565-568) wherein the genetic therapy administers a drug (i.e., the gene encoding p53 which p53 protein as regulatory effect) which is the gene since the drug for a genetic therapy is a DNA/gene as well as combined approaches (Moossa *et al.* at page 610+) as well as page 1572 which indicates suggests using genetic therapy by replacing the normal fragment of the gene to prevent development of the disease as for example indicated in the combined cited references. Thus, there is in the combined references, suggestion and motivation to combine the steps even if not stated identically to the wording of the claims; and, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 1, 2, 4-15 and 17-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nabel *et al.* (US 5,328,470) taken with Wu *et al.* (US 5,166,320), Malkin *et al.* (Science), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2).

Nabel *et al.* disclosed genetic therapy by transforming cells *in vivo* to treat malignancies (col 11-12) by inhibiting tumor cell growth by gene transfer directly into the tumor cells where (1) the transforming DNA induced rejection, regression or both of the tumor (col 12, lines 45+); (2) the vector is a liposome complex and/or conjugated with for example polylysine (col 11, line 15+ and col 14, line 60+) whereas the Wu *et al.* reference disclosed a process for *in vivo* delivery (as for example intravenous injection, i.e., a direct injection wherein injection into an artery is an obvious variation of injection into a vein) of DNA to a target cell (see for example col 11, and the abstract as to polylysine) using a complex of asialoglycoprotein to hepatoma cells and for replacement of "defective genes" responsible for inherited diseases as for example where there are familial germline mutations of cancer where mutations in the DNA encoding p53 have been shown to be transmitted via the germline (see Malkin *et al.*, the abstract and pages 1234-1238) and/or in a virus such as derived from adenovirus, papilloma virus, herpes virus, or parvovirus (col 13); (3) the DNA is for example p53 (col 14 and 18); where (4) the reference indicates that the function of the transforming DNA is in one instance

antagonize by overexpression, the function or other activities of a gene in the animal or patient (col 10) such as to suppress an endogenous gene (col 1 of Nabel *et al.* wherein Malkin *et al.* indicate that the endogenous gene is p53 which is defective, it would have been obvious to suppress expression of a defective endogenous p53 gene by replacement with the form of the gene which is not defective and thereby suppress the effect of the defective gene) which is for example a tumor antigen (col 18) indicated as a mutant p53 oncogene that where Malkin *et al.* disclose that p53 mutations are transmitted via the germline in familial breast cancer, sarcomas, and other neoplasms, it would have been obvious to one of ordinary skill in the art from at least the motivating reasons of cancer suppression (Nabel *et al.*) to have used the wild-type p53 to suppress as for example by blocking the effect of the mutant gene by providing the normal function of p53 by using as the DNA the encoding the wild-type p53 to alleviate the effects of the genetic predisposition to certain forms of inherited cancer which would have altered the effect of known routine cancer treatment regimes which would have been obvious to anyone of ordinary skill in the art to do and which treatment regimes included radiation therapy (as for example Moossa *et al.* at pages 477, 1138, 1140, and 1170), chemotherapy (as for example Moossa *et al.* at pages 527-536, 565-568, 1098, 1140, and 1572), biological therapy (as for example Moossa *et al.* at pages 607-612 using biological response modifiers), cryotherapy (as for example Moossa *et al.* at pages 1098, 1170, 1329, 1368, and 1569-1570), and hyperthermia (as for example Moossa *et al.* at page 1139-1149) are known treatment methods, have been successfully used, and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent (as for example via an artery (page 590) or a (page 591) body cavity or by IV as for example indicated at page 592) and would have resulted in the process wherein a DNA encoding a tumor sensitizing product would have been delivered to an afflicted individual along with routine known and established appropriate therapies (radiation therapy, chemotherapy, biological therapy, cryotherapy, and hyperthermia therapy in one or more combinations) for treatment of cancers. Here, the Moossa *et al.* reference (page 530) indicated that because there are such narrow margins between effective and toxic dosages for many antineopplastic agents, rational therapy should be assisted by the ability to maintain drug concentrations in the specified therapeutic ranges. Such assist "the ability to maintain drug concentrations in the specified therapeutic ranges" is what anyone of ordinary skill in the art would expect if not anticipate from combinatorial therapy (Moossa *et al.* at pages 565-568) wherein the genetic therapy administers a drug (i.e., the gene encoding p53 which p53

protein as regulatory effect) which is the gene since the drug for a genetic therapy is a DNA/gene as well as combined approaches (Moossa *et al.* at page 610+) as well as page 1572 which indicates suggests using genetic therapy by replacing the normal fragment of the gene to prevent development of the disease as for example indicated in the combined cited references. Thus, there is in the combined references, suggestion and motivation to combine the steps even if not stated identically to the wording of the claims.Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claim 23 (directed to an aerosolized preparation) stands rejected under 35 U.S.C. 103(a) as being unpatentable over either of Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1, 2, 4-11 and 17-20 above;

or,

under 35 U.S.C. 103(a) as being unpatentable over Nabel *et al.* (US 5,328,470) taken with Wu *et al.* (US 5,166,320), Malkin *et al.* (Science), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1, 2, 4-11 and 17-20 above, each further in view of Eppstein *et al.* US 5,366,737).

Cheng *et al.* (Cancer Res.), Srivastava, and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) and here, where Cheng *et al.* discusses using the DNA encoding p53 to effect cancer suppression, it would have been obvious to one of ordinary skill in the art to have also used an aerosol preparation of DNA for aerosol/spray delivery as disclosed in the Eppstein *et al.* patent (col 13). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Alternatively, where Nabel *et al.* and Malkin *et al.* (Science) discuss cancer suppression, p53, and genetic therapy with discussion of the familial inheritance, it would have been obvious to one of ordinary skill in the art to have also used an aerosol preparation of DNA for aerosol/spray delivery as disclosed in the Eppstein *et al.* patent (col 13) for delivery, for example, to lung cancer cells. In either situation above, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

(12) New Ground(s) of rejection.

This examiner's answer does not contain any new ground of rejection.

(13) Response to Argument.

The commentary in the Appeal brief has been noted and considered but is not persuasive. Insofar as this examiner's answer does not contain the stated rejection under 35 U.S.C. 112 first paragraph nor the rejection under 35 U.S.C. 112 second paragraph, the rejections are removed. The comments regarding these rejections in appellant's brief are moot in view of the foregoing.

In view of the cancellation of claims 3, 21, and 22, the above stated rejections have been modified to recite only the appealed claims and are not new grounds of rejection.

The rejection of claim 21 under 35 U.S.C. 103 as being unpatentable over either of Cheng *et al.* (Cancer Res.) taken with Srivastava (US '749), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1-11, 17-20, and 22 above; or under 35 U.S.C. 103 as being unpatentable over Nabel *et al.* (US '470) taken with Wu *et al.* (US '320), Malkin *et al.* (Science), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1-15, 17-20 and 22 above, and further in view of Itoh *et al.* (Cell), is removed solely in view of the cancellation of the claim.

It is also pointed out that appellant's brief does not contain in the section "ARGUMENT" in item "III. CLAIMS 1, 2, 4-40, AND 23 ARE NOT OBVIOUS IN VIEW OF THE REFERENCES CITED BY THE EXAMINER", a separate discussion for each stated ground of rejection as required by 37 C.F.R. 1.192.

The four rejections under 35 U.S.C. 103(a) stated above remain. Appellant's comments in the brief at pages 16-25 to the grounds of rejection are discussed below. Of note is that the paragraph spanning pages 16-17 is only a statement of the claims and references cited in each of the stated rejections. This paragraph does not *per se* contain any discussion traversing any stated ground of rejection even where the last sentence asserts failure to support a *prima facie* case because this paragraph presents no scientific factually based reasons in support of the assertion.

The appeal brief at pages 17-19, item "III A. The References Cited By The Examiner" set forth appellant's brief summary of the references cited in the stated rejections except that the Itoh *et al.* reference is not used in the presently stated rejections because claim 21 has been canceled. Appellant's brief summary of the references is incomplete as is evident from the reasons set forth in the stated rejections in which the references are cited.

The appeal brief at pages 19-22, item "III B, asserts that the references fail to support *prima facie* obviousness and cited *In re Gulack* (as to evaluating all limitations of a claim), *In re Fine* (as to suggestion and/or incentive), *In re Laskowski* and the *In re Dow Chemical Co.* (the latter two as to motivation/suggestion being from a source other than applicant's disclosure) decisions in support.

Page 19 of appellant's brief starting from the beginning of III B. to the end of the last full paragraph cites *In re Gulack* as to evaluating all limitations of a claim and presents part of appealed claim 1 but adds limitations found in the dependent claims 2-8 by recitation of radiation therapy, chemotherapy, biological therapy, cryotherapy, or hyperthermia. The limitations of the dependent claims are not *per se* found in claim 1. Thus, it is apparent that this segment of appellant's brief does not apply solely any one single stated ground of rejection. The commentary, however, is noted but is not persuasive because the claims have been evaluated as a whole, i.e., all of the limitations considered, as discussed in each separately stated ground of rejection.

In view of the foregoing, the standing rejections remain for the reasons discussed in the prior Office Actions and as discussed below.

(A) The rejection of claims 1, 2, 4-11, and 17-20 under 35 U.S.C. 103(a) as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2).

Insofar as the paragraph bridging pages 19-20, appellant's brief discussed the Cheng *et al.*, Srivastava, and Moossa *et al.* references and asserted that there is no indication of combining the two steps to increase the therapeutic effect. The comment is not persuasive because combinatorial therapies are known and clinically practiced and it would have been obvious to one of ordinary skill in the art to have (1) used known vectors and processes demonstrated as effective that are known to function *in vivo* for delivery of known DNA encoding wild-type p53 for which the Srivastava reference

disclosed vectors that are safe for gene therapy to; (2) reduced/eliminated factors in the potential problem of heterologous DNA effecting unwanted effects which would have motivated one of ordinary skill in the art; (3) used the teachings and vectors and modifications thereto such as disclosed in the Srivastava patent which at col 3 indicated the vectors are for bone marrow cells, i.e., like those of the Cheng *et al.* reference); and (4) used virus such as an adeno, herpes, or vaccinia virus (see col 3) for delivery of DNA encoding, for example, p53 or Rb(col 6) for treatment of cancer (col 6). Moreover, where the Cheng *et al.* reference referred to bone marrow transplantation regimes it would have been obvious to any one of ordinary skill in the art that radiation therapy (as for example Moossa *et al.* at pages 477, 1138, 1140, and 1170), chemotherapy (as for example Moossa *et al.* at pages 527-536, 565-568, 1098, 1140, and 1572), biological therapy (as for example Moossa *et al.* at pages 607-612 using biological response modifiers), cryotherapy (as for example Moossa *et al.* at pages 1098, 1170, 1329, 1368, and 1569-1570), and hyperthermia (as for example Moossa *et al.* at page 1139-1149) are known treatment methods, have been successfully used, and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent (as for example via an artery (page 590) or a (page 591) body cavity or by IV as for example indicated at page 592).

Moreover, where appellant's brief asserts that none of the references described a gene that made the cells more susceptible to conventional cancer therapy but it is not persuasive since Cheng *et al.* used p553 to facilitate suppression of the tumorigenic phenotype (see at least the abstract. Here, the Wu *et al.*, and Srivastava references set forth methods of therapy using DNA constructs and indicated that DNA encoding p53 (among other proteins) should be used and make the method step in the claimed therapy known in the art prior to the time the claimed invention was made. Here Moossa *et al.* disclosed chemotherapy, biological therapy using biological response modifiers -p53 is a known biological response modifier), cryotherapy, and hyperthermia are known treatment methods, have been successfully used, and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent as for example via an artery or a body cavity or by IV and would have resulted in the step of conventional cancer therapy joined to a process wherein a DNA encoding p53 or other genes which encode tumor sensitizing products would have

been delivered to an afflicted individual along with routine known and established appropriate therapies (radiation therapy, chemotherapy, biological therapy, cryotherapy, and hyperthermia therapy in one or more combinations) for treatment of cancers. Thus, the comments are not persuasive when the invention is evaluated as a whole and the citation of *In re Gulak* is not persuasive of appellant's position because when the cited references are considered as a whole, there are no differences. The effects of the therapy using the DNA are expected to have the same effect (the same DNA should produce the same effects, not different effects) of sensitizing the cells and the cancer therapy is expected to have the known and expected cancer cell killing effects. Thus, the therapy using p53 in combination with conventional therapies is expected to have the same effect as disclosed in the references and the conventional therapies used with the gene therapy for p53 is expected as for example disclosed in the Moossa *et al.* reference is expected to the same effect as when used alone. Thus, each form of therapy is expected to have its own addition to the effect of the therapy and each together is expected to at least have an additive effect. The additive effect is an increased therapeutic effect over each of the therapies alone. Moreover, where not all of the tumor cells are transfected to produce wild-type p53, the conventional therapies set forth in the Moossa *et al.* reference are still expected to act on the tumorigenic cells and thereby produce the known effect of killing of tumor cells which is additive to the effect of the p53 genetic based therapy. Thus, in either instance, the combinatorial therapy is expected to produce an increased therapeutic effect. Of note is that the Moossa *et al.* reference (page 530) indicates that because there are such narrow margins between effective and toxic dosages for many antineopplastic agents, rational therapy should be assisted by the ability to maintain drug concentrations in the specified therapeutic ranges. Such assist "the ability to maintain drug concentrations in the specified therapeutic ranges" is what anyone of ordinary skill in the art would expect if not anticipate from combinatorial therapy (Moossa *et al.* at pages 565-568) wherein the genetic therapy administers a drug (i.e., the gene encoding p53 which p53 protein as regulatory effect) which is the gene since the drug for a genetic therapy is a DNA/gene as well as combined approaches (Moossa *et al.* at page 610+) as well as page 1572 which indicates suggests using genetic therapy by replacing the normal fragment of the gene to prevent development of the disease as for example indicated in the combined cited references. Thus, there is in the combined references, suggestion and motivation to combine the steps even if not stated identically to the wording of the claims. Thus, the comments in this paragraph are not persuasive as the claims have been considered as a whole.

In the first full paragraph of page 20, appellant's brief asserts there is no motivation and cites the *In re Fine* and *In re Laskowski* decisions as to suggestion and/or incentive for combining the references. The comment this paragraph is not persuasive for the reasons stated in the ground of rejection and for the reasons in the preceding paragraphs. See *In re Gorman*, 18 USPQ2d 1885 (CA FC 1991) where it is indicated that the criterion is what the references would have meant to a person of ordinary skill in the field of the invention. The number of cited references does not negate the obviousness of the combination, for the prior art uses the various elements for the same purposes as they are used by appellants, making the claimed invention as a whole obvious in terms of 35 U.S.C. 103(a) especially where the elements exist as analogous art and are pertinent to the problem (cancer therapy) which the inventor is concerned and when the references are in the same of analogous fields (cancer therapy, knowledge thereof by the hypothetical person of ordinary skill in the art (the clinical research oncologist molecular biologist) is presumed. Attention is also directed to *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) where as here, it is *prima facie* obvious to combine two processes (each directed to cancer therapy) instead of compositions, where each process is taught by the prior art to be useful for same purpose (cancer therapy) in order to effect a process that is used for the very same purpose - cancer therapy. The idea of combining them flows logically from their having been individually taught in prior art for the identical purpose of treating cancer where the combined references discuss and suggest and used combinatorial therapies. Claims that require no more than putting the two processes together (i.e., mixing of the components, which are in this instance, the two processes) set forth *prima facie* obvious subject matter. In view of the foregoing, appellant's citation of the *In re Fine* and *In re Laskowski* decisions and the comments in the first full paragraph of page 20 are not persuasive.

The paragraph spanning pages 20-21 refers to the references by Chen *et al.*, Wu *et al.*, Eppstein *et al.*, Nabel *et al.*, and Itoh *et al.* (not part of any stated rejection in this answer since claim 21 was canceled). None of these references *per se* are part of the above rejection of claims 1, 2, 4-11, and 17-20 under 35 U.S.C. 103(a) as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2). The paragraph spanning pages 20-21 therefore, is not further discussed as part of the above ground of rejection.

The last full paragraph of page 21 and the paragraph spanning pages 21-22 assert hindsight and cited the *In re Dow Chemical Co.* decision as to motivation/suggestion being from a source other than applicant's disclosure. The comments are not persuasive because no hindsight is needed or required to combine the Cheng *et al.* disclosure teachings of genetic therapy with that of the Srivastava patent nor the Moossa *et al.* reference for the reasons indicated in the stated rejection. Known treatment methods have been successfully used and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent. The Moossa *et al.* reference disclosed chemotherapy, biological therapy using biological response modifiers -p53 is a known biological response modifier), cryotherapy, and hyperthermia are known treatment methods, have been successfully used, and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent as for example via an artery or a body cavity or by IV and would have resulted in the step of conventional cancer therapy joined to a process wherein a DNA encoding p53 or other genes which encode tumor sensitizing products would have been delivered to an afflicted individual along with routine known and established appropriate therapies (radiation therapy, chemotherapy, biological therapy, cryotherapy, and hyperthermia therapy in one or more combinations) for treatment of cancers. The effects of the therapy using the DNA are expected to have the same effect (the same DNA should produce the same effects, not different effects) of sensitizing the cells and the cancer therapy is expected to have the known and expected cancer cell killing effects. Thus, the therapy using p53 in combination with conventional therapies is expected to have the same effect as disclosed in the references and the conventional therapies used with the gene therapy for p53 is expected as for example disclosed in the Moossa *et al.* reference is expected to the same effect as when used alone. Thus, each form of therapy is expected to have its own addition to the effect of the therapy and each together is expected to at least have an additive effect. The additive effect is an increased therapeutic effect over each of the therapies alone. Moreover, where not all of the tumor cells are transfected to produce wild-type p53, the conventional therapies set forth in the Moossa *et al.* reference are still expected to act on the tumorigenic cells and thereby produce the known effect of killing of tumor cells which is additive to the effect of the p53 genetic based therapy. Thus, in either instance, the combinatorial therapy is expected

to produce an increased therapeutic effect. Of note is that the Moossa *et al.* reference (page 530) indicates that because there are such narrow margins between effective and toxic dosages for many antineopplastic agents, rational therapy should be assisted by the ability to maintain drug concentrations in the specified therapeutic ranges. Such assist "the ability to maintain drug concentrations in the specified therapeutic ranges" is what anyone of ordinary skill in the art would expect if not anticipate from combinatorial therapy (Moossa *et al.* at pages 565-568) wherein the genetic therapy administers a drug (i.e., the gene encoding p53 which p53 protein as regulatory effect) which is the gene since the drug for a genetic therapy is a DNA/gene as well as combined approaches (Moossa *et al.* at page 610+) as well as page 1572 which indicates suggests using genetic therapy by replacing the normal fragment of the gene to prevent development of the disease as for example indicated in the combined cited references. Thus, there is in the combined references, suggestion and motivation to combine the steps even if not stated identically to the wording of the claims. The reasons for combining the references are found in sources which are not appellant's disclosure, and, comments regarding hindsight are not persuasive nor based upon logical deduction. Thus, the *In re Dow Chemical Co.* decision citation is not persuasive. Neither the facts nor fact pattern in the present application are that of the cited decision nor parallel to the facts of the *In re Dow Chemical Co.* decision. In view of the foregoing, the comments in appellant's brief as to the stated rejection are not persuasive.

(B) The rejection of claims 12-18, and 20 under 35 U.S.C. 103(a) as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1, 2, 4-11, and 17-20 above and further in view of Wu *et al.* (US 5,166,320) and Malkin *et al.* (Science) and Chen *et al.* (Oncogene).

The above stated rejection combined the Cheng *et al.*, Srivastava, and Moossa *et al.* with Wu *et al.*, Malkin *et al.* and the Chen *et al.* references. The paragraph spanning pages 20-21 discussed the Itoh *et al.* reference and the Fas antigen. The Itoh *et al.* reference is not *per se* part of any stated rejection in this answer since claim 21 was canceled; and, commentary regarding same is not persuasive nor germane to any appealed claim.. The paragraph spanning pages 20-21 discussed the Chen *et al.*, Wu *et al.*, Eppstein *et al.*, and Nabel *et al.* references. The Eppstein *et al.* and Nabel *et al.* references, however, are not formally part of the stated rejection.

The paragraph spanning pages 20-21 paragraph asserts that the Cheng *et al.* reference did not describe using wild-type p53 to make tumor cells more sensitive to chemotherapy or radiation and that Wu *et al.* (as the only additional reference referred to in this paragraph of appellant's brief that is formally part of the stated rejection) described methods of delivering genes but did not deliver a gene encoding p53. The comments are not persuasive because where appellant asserts the Cheng *et al.* reference did not describe using wild-type p53 to make tumor cells more sensitive to chemotherapy or radiation, the Moossa *et al.* reference as in the preceding paragraphs did indicate and teach combinatorial therapy where the combined references of Cheng *et al.*, Srivastava and Moossa *et al.* result in the claimed process for the reasons indicated in the preceding paragraphs. As to the discussion of the Wu *et al.* patent in this paragraph, the comment is not persuasive because the Wu *et al.* reference was cited for disclosure of a process of *in vivo* delivery (as for example intravenous injection, i.e., a direct injection wherein injection into an artery is an obvious variation of injection into a vein) of DNA to a target cell (see for example col 11, and the abstract as to polylysine) using a complex of asialoglycoprotein to hepatoma cells and for replacement of "defective genes" responsible for inherited diseases as for example where there are familial germline mutations of cancer where mutations in the DNA encoding p53 have been shown to be transmitted via the germline (see Malkin *et al.*, the abstract and pages 1234-1238) and where Cheng *et al.* (Cancer Res.) indicate that providing DNA encoding wild-type p53 to cells that have defective or no expression of p53 with subsequent expression of that DNA encoding wild-type p53 effects reduced tumorigenicity (see page 1803), it would have been obvious to one of ordinary skill in the art to combine the teachings of Cheng *et al.* (Cancer Res.) taken with Srivastava, Moossa *et al.* with Wu *et al.*, Malkin *et al.* and Chen *et al.* (Oncogene) for treatment of cancer and directed delivery of the DNA encoding for example p53 to effect reduced tumorigenicity and reduced frequency of posttransplantation relapse. Thus as to delivery of a gene encoding a wild-type p53 protein, the cited combined references do teach delivery thereof and the expected effect. In view of the foregoing, the comments in the paragraph spanning pages 20-21 are not persuasive as to the stated ground of rejection.

The comments in appellant's brief (item III C) pages 22-23 discuss the Cheng *et al.* and the Chen *et al.* references together. The sole ground of rejection where both references appear together is the rejection of claims 12-18, and 20 under 35 U.S.C. 103(a) as being unpatentable over Cheng *et al.*

(Cancer Res.) taken with Srivastava (US 5,252,479), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1, 2, 4-11, and 17-20 above and further in view of Wu *et al.* (US 5,166,320) and Malkin *et al.* (Science) and Chen *et al.* (Oncogene). Thus the comments discussing both of these references in item III C of appellant's brief appear in this section of the examiner's answer.

The first full paragraph under item III C (page 22) in appellant's brief asserts the "motive" in both the Cheng *et al.* and Chen *et al.* references is to use p53 to reduce the growth rate of tumor cells and argues that the tumor suppression effect is different from that of therapy sensitization. It is not necessary for the prior art "motive" to be identical to that asserted by appellant. See *In re Nilssen*, 7 USPQ2d 1500 (CA FC 1988) which indicated the hypothetical person of ordinary skill in the art is assumed to have knowledge of all prior art in the field of the inventor's endeavor, of prior art solutions for a common problem even if outside the field, and that for the purposes of combining references, those references need not explicitly suggest combining teachings. The comment is not persuasive because in both tumor suppression and in therapy sensitization as presently claimed, a wild-type p53 gene is administered as part of a genetic construct. In both instances, the gene is identical. None of appellant's prior comments nor appellant's brief nor appellant's specification describe a gene that is any different. The same gene is used, the same effects are expected. The same gene can only produce the same protein product. Thus, appellant's asserted wild-type p53 gene is the same as the prior art p53 gene. Appellant's wild-type p53 gene product, the p53 protein is identical to the p53 protein in the prior art. The identical protein is expected to produce the identical effects, not different effects. A product and its properties are inseparable and applicant has not demonstrated that tumor suppression is separable from therapy sensitization.

Moreover, where the first full paragraph under item III C (page 22) in appellant's brief asserts sensitization, the instant claims are not directed to sensitization. The claims recite "increasing the therapeutic effect of a cancer therapy". Decreasing the amount of tumor cells by altering the tumorigenic phenotype to that of a normal cell by administering a gene which encoded a wild-type p53 protein reduces the tumor burden, i.e., translates to fewer cells with a tumorigenic phenotype. Known clinically routine cancer therapies also reduce tumor burden by killing tumor cells, i.e., reduction of tumor burden. Given the motivation as stated in the preceding paragraphs and in the stated rejections, it is readily evident that administering a gene which encoded a wild-type p53 protein reduced the tumor

burden and that known clinically routine cancer therapies also reduce tumor burden each of which are at least additive in effect and therefore do result in increasing the therapeutic effect of reduction of tumor burden which is the desired effect of any cancer therapy. Thus, it is apparent that the comments in appellant's brief (page 21 first paragraph under item III C and the paragraph bridging pages 22-23 are not persuasive.

Insofar as the paragraph bridging pages 22-23 and the first full paragraph of page 23 assert that one of ordinary skill in the art is led to believe that the p53 genetic therapy makes the cells more resistant to conventional tumor therapies, the comment is noted but not persuasive since the cells containing the heterologous gene construct for and expressing wild-type p53 have suppressed tumor cell phenotype, i.e., these cells appear to have a "normal" cell phenotype. Thus, the cells expressing wild-type p53 have suppressed tumor cell phenotype which effectively a "normal" cell phenotype. Cancer therapy is not directed to killing "normal" cells, however, where not all cancer cells are effectively transformed, the remaining cancer cells with no heterologous genetic material are more easily treated due to sensitivity to known clinical regimens (note appellant's discussion at page 24 of the instant brief on appeal). Thus, the effect is one of increasing the effect of the cancer therapy. In this regard, the citation of *In re Grasselli* (brief page 23, last full paragraph) is not persuasive since the combined references do not teach away from the claimed invention nor are the facts the same as there is in this instance no express prohibition against inclusion (*In re Grasselli*, at page 780) nor is this an instance of substitution of a catalyst but, one where it is expected that result A (genetic therapy which provided a gene encoding and expressing a wild-type p53 protein for which the expected result is a reduction in tumor burden) and a treatment using known routine clinical oncology treatments, both are for cancer therapy and both have a demonstrated expectation of reduction in/of tumor burden. Thus, appellant's citation of *In re Grasselli* is not persuasive.

(C) The rejection of claims 1, 2, 4-15, and 17-20 under 35 U.S.C. 103(a) as being unpatentable over Nabel *et al.* (US 5,328,470) taken with Wu *et al.* (US 5,166,320), Malkin *et al.* (Science), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2).

The above stated rejection combined the Nabel *et al.*, Wu *et al.*, Mallkin *et al.* and Moossa *et al.* references. The paragraph spanning pages 20-21 discussed the Itoh *et al.* reference and the Fas antigen which are not *per se* part of any stated rejection in this answer since claim 21 was canceled.

Thus, commentary regarding the Itoh *et al.* and the Fas antigen is not persuasive nor germane to any appealed claim. The Chen *et al.* and Eppstein *et al.* references which are not formally part of the stated rejection and are not further discussed as part of this ground of rejection.

Where the above stated rejection combines Nabel *et al.*, Wu *et al.* Mallkin *et al.* and Moossa *et al.*, the paragraph spanning pages 20-21 discusses the Wu *et al.* and Nabel *et al.* references with the assertion that Wu *et al.* and Nabel *et al.* "described methods for delivering genes or proteins to cells but did not describe delivering a wild-type p53 gene", the comments are not persuasive because as stated in the ground of rejection, where both Nabel *et al.* and Wu *et al.* disclosed genetic therapy and processes therefor and where the Malkin *et al.* reference indicated endogenous gene is p53 is defective, it would have been obvious to suppress expression of a defective endogenous p53 gene by replacement with the form of the gene which is not defective and thereby suppress the effect of the defective gene) which is for example a tumor antigen (col 18) indicated as a mutant p53 oncogene that where Malkin *et al.* disclose that p53 mutations are transmitted via the germline in familial breast cancer, sarcomas, and other neoplasms. Thus, it would have been obvious to one of ordinary skill in the art from at least the motivating reasons of cancer suppression (Nabel *et al.*) to have used the wild-type p53 to suppress as for example by blocking the effect of the mutant gene by providing the normal function of p53 by using as the DNA the encoding the wild-type p53 to alleviate the effects of the genetic predisposition to certain forms of inherited cancer which would have altered the effect of known routine cancer treatment regimes which would have been obvious to anyone of ordinary skill in the art to do. Known treatment regimes included radiation therapy, chemotherapy, biological therapy (using biological response modifiers), cryotherapy, and hyperthermia have been successfully used, and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent and would have resulted in the process wherein a DNA encoding a tumor sensitizing product would have been delivered to an afflicted individual along with routine known and established appropriate therapies (radiation therapy, chemotherapy, biological therapy, cryotherapy, and hyperthermia therapy in one or more combinations) for treatment of cancers. Thus the comments regarding the Nabel *et al.* and Wu *et al.* references are not persuasive.

(D) The rejection of claim 23 (as directed to an aerosolized preparation) under 35 U.S.C. 103(a) as being unpatentable over either of Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1-11, 17-20, and 22 above;

or,

under 35 U.S.C. 103(a) as being unpatentable over Nabel *et al.* (US 5,328,470) taken with Wu *et al.* (US 5,166,320), Malkin *et al.* (Science), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1, 2, 4-15 and 17-20 above, each further in view of Eppstein *et al.* US 5,366,737).

The above stated rejection of claim 23 combined the Cheng *et al.*, Srivastava, and Moossa *et al.* references and in the alternative the Nabel *et al.*, Wu *et al.*, Malkin *et al.*, and Moossa *et al.* references with that of the Eppstein *et al.* reference. The paragraph spanning pages 20-21 discussed the Itoh *et al.* reference and the Fas antigen but the reference is not *per se* part of any stated rejection in this answer since claim 21 was canceled. Thus, commentary regarding the Itoh *et al.* and the Fas antigen is not persuasive nor germane to any appealed claim.

Where the above stated rejection combined the Cheng *et al.*, Srivastava, and Moossa *et al.* references and in the alternative the Nabel *et al.*, Wu *et al.*, Malkin *et al.*, and Moossa *et al.* references with that of the Eppstein *et al.* reference, the comments regarding the Eppstein *et al.* reference are not persuasive for the reasons indicated in the preceding paragraphs.

As to the Eppstein *et al.* reference, appellant's response asserts that the reference described methods of delivering genes but not a gene encoding p53. The comment is not persuasive nor does it address the reason stated in the ground of rejection for the citation of the Eppstein *et al.* reference which was that Cheng *et al.*, Srivastava, and Moossa *et al.* and here, where Cheng *et al.* discusses using the DNA encoding p53 to effect cancer suppression, it would have been obvious to one of ordinary skill in the art to have also used an aerosol preparation of DNA for aerosol/spray delivery as disclosed in the Eppstein *et al.* patent (col 13). Thus, the comments in the paragraph spanning pages 20-21 in appellant's brief are not persuasive.

As to each of the four (4) stated rejections, the comments in item III D (brief pages 24-25) have been considered as to the assertion of "unexpected results", however, it is apparent that the results appellant argues as unexpected are not found in the appealed claims. Reading limitations into the

claims is an inappropriate interpretation of the claims - *In re Zletz*, 13 USPQ2d 1320 (CA FC 1989), which clearly stated that there is no reason to read into the claim(s) limitations of the specification (or for that matter from anywhere else). As discussed in the preceding paragraphs, the results required of the appealed claims are not unexpected. Attention is directed to the above discussion of item III C which is addressed in the discussion of the Cheng *et al.* and the Chen *et al.* references in the rejection of claims 12-18, and 20 under 35 U.S.C. 103(a) as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US 5,252,479), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1, 2, 4-11, and 17-20 above and further in view of Wu *et al.* (US 5,166,320) and Malkin *et al.* (Science) and Chen *et al.* (Oncogene).

It is noted that the three full paragraphs of page 24 in appellant's brief refer to figures 1 and 2 and example 4 and 5 of the present application and cited the *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Company et al.* as to unexpected results and assert that figure 1 and example 4 show tumor cells with heterologous genetic material encoding p53 as more sensitive to cisplatin and that figure 2 and example 5 show tumor cells as more sensitive to radiation therapy. The third full paragraph refers to a reference by Vogelstein *et al.* and is stated to be "a prior art reference" and quoted therefrom by indication that the p53 mutations increase rather than decrease the sensitivity to antitumor agents.

As to the above, no claims on appeal recite treatment with cisplatin nor do any claims recite the identical vector used in example 4 nor do any claims recite the identical process in example 4. Thus, where appellant's assert unexpected property, the specific treatment is not recited in any appealed claims. Similarly, no claims recite the identical vector used in example 5 nor do any claims recite the identical process and conditions in example 5. Appellant's comments citing the *Lindemann Maschinenfabrik v. American Hoist & Derrick Co.* decision for unexpected/surprising results, however, as pointed out above, the asserted effect is that produced by the wild-type gene product that is encoded by the wild-type gene. The same gene is expected to produce the same effective product that has the same effect. Neither the present application nor any of applicant's responses demonstrate that the wild-type gene is any different from the cited art. Thus, the comments in the response are not persuasive. Insofar as page 24 refers to cisplatin treatment as more effective in cells with wild-type p53 than in cells lacking same is contrary to applicant's own use of the Vogelstein *et al.* reference

teaching of "p53 mutations may therefore constitute one of the few alterations that increase rather than decrease the sensitivity of cells to antitumor agents". Key to the Vogelstein *et al.* reference is that it discusses mutations to p53. It does not state what happens when wild-type p53 placed back into that tumor cell. As to the asserted results not being reported or inferred in the references, the instant claims do not both indicate cisplatin and radiation. Thus, appellant's arguments are not persuasive.

(14) Period of response to new ground of rejection.

This answer contains no new ground of rejection. No period of response is set. Prosecution remains closed.

(15) Request for oral hearing.

Appellant's request for an oral hearing (paper number 18, filed 24 April 1997) is noted. Notification as to date and time will be made under separate cover.

For the above reasons, it is believed that the rejections should be affirmed.

Respectfully submitted,

Christopher S. F. Low

Christopher Low
1 August 1997

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800